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C12Q 1/68, G06F 17/50 // C12N 9/86, 9/42

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(22) International Filing Date: 15 October 1999 (15.10.1999)

(25) Filing Language: English

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Not furnished 8 October 1999 (08.10.1999) US

(71) Applicant: **XENCOR, INC.** [US/US]; 2585 Nina Street,
Pasadena, CA 91107-3708 (US).

(72) Inventors: **FIEBIG, Klaus, M.**; Grosse Eschenheimer
Street 41A, D-60313 Frankfurt (DE). **HAYES, Robert,**
J.; 1848 Vistillas Road, Altadena, CA 91006 (US).
DAHIYAT, Bassil, I.; 4413 San Andreas Avenue, Los An-
geles, CA 90065 (US). **BENTZIEN, Jörg**; 277 Pleasant
Street #307, Pasadena, CA 91101 (US).

(74) Agents: **TRE CARTIN, Richard, F.** et al.; Flehr, Ho-
hbach, Test, Albritton & Herbert LLP, Suite 3400, 4 Em-
barcadero Center, San Francisco, CA 94111-4187 (US).

(81) Designated States (*national*): AE, AL, AM, AT, AU, AZ,
BA, BB, BG, BR, BY, CA, CH, CN, CU, CZ, DE, DK, EE,
ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP,
KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MD,
MG, MK, MN, MW, MX, NO, NZ, PL, PT, RO, RU, SD,
SE, SG, SI, SK, SL, TJ, TM, TR, TT, TZ, UA, UG, UZ,
VN, YU, ZA, ZW.

(84) Designated States (*regional*): ARIPO patent (GH, GM,
KE, LS, MW, SD, SL, SZ, TZ, UG, ZW), Eurasian patent
(AM, AZ, BY, KG, KZ, MD, RU, TJ, TM), European patent
(AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU,
MC, NL, PT, SE), OAPI patent (BF, BJ, CF, CG, CI, CM,
GA, GN, GW, ML, MR, NE, SN, TD, TG).

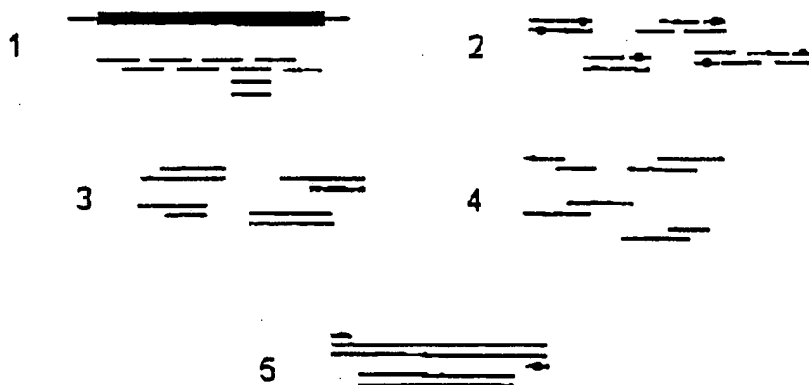
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13 December 2001

*For two-letter codes and other abbreviations, refer to the "Guid-
ance Notes on Codes and Abbreviations" appearing at the begin-
ning of each regular issue of the PCT Gazette.*

(54) Title: PROTEIN DESIGN AUTOMATION FOR PROTEIN LIBRARIES



(57) Abstract: The invention relates to the use of protein design automation (PDA) to generate computationally prescreened sec-
ondary libraries of proteins, and to methods and compositions utilizing the libraries.

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INTERNATIONAL SEARCH REPORT

International Application No
PCT/US 99/24229

A. CLASSIFICATION OF SUBJECT MATTER

IPC 7 C12N15/10 C12Q1/68 G06F17/50 //C12N9/86,C12N9/42

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)

IPC 7 C12N C12Q G06F

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)

WPI Data, PAJ, CAB Data, STRAND, EPO-Internal

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
E	WO 00 68396 A (XENCOR INC) 16 November 2000 (2000-11-16) cited in the application page 17, line 21 -page 26, line 20; example 5	1-9
P, X	WO 98 47089 A (CALIFORNIA INST OF TECHN) 22 October 1998 (1998-10-22) page 6, line 26 - line 30 ----- -/--	1

☒ Further documents are listed in the continuation of box C.

☒ Patent family members are listed in annex.

* Special categories of cited documents:

- *A* document defining the general state of the art which is not considered to be of particular relevance
- *E* earlier document but published on or after the international filing date
- *L* document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)
- *O* document referring to an oral disclosure, use, exhibition or other means
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- *X* document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone
- *Y* document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art.
- *G* document member of the same patent family

Date of the actual completion of the international search

27 February 2001

Date of mailing of the international search report

05/03/2001

Name and mailing address of the ISA

European Patent Office, P.B. 5818 Patentlaan 2
NL - 2280 HV Rijswijk
Tel. (+31-70) 340-2040, Tx. 31 651 epo nl,
Fax: (+31-70) 340-3016

Authorized officer

Hornig, H

INTERNATIONAL SEARCH REPORT

International Application No

PCT/US 99/24229

C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
A	DAHIYAT B I ET AL: "PROTEIN DESIGN AUTOMATION" PROTEIN SCIENCE, GB, CAMBRIDGE UNIVERSITY PRESS, CAMBRIDGE, vol. 5, no. 5, 1 May 1996 (1996-05-01), pages 895-903, XP002073372 ISSN: 0961-8368 cited in the application the whole document	
X	--- WO 98 32845 A (CRIPPS JOANNA E ;SOEDERLIND ULF HANS ESKIL (SE); BIOINVENT INT AB) 30 July 1998 (1998-07-30) the whole document	7,8
X	--- WO 95 22625 A (AFFYMAX TECH NV ;CRAMERI ANDREAS (US); STEMMER WILLEM P C (US)) 24 August 1995 (1995-08-24) the whole document -----	7,8

Information on patent family members

International Application No

PCT/US 99/24229

Patent document cited in search report	Publication date	Patent family member(s)	Publication date
WO 0068396 A	16-11-2000	AU 5132700 A	21-11-2000
WO 9847089 A	22-10-1998	AU 6965498 A EP 0974111 A	11-11-1998 26-01-2000
WO 9832845 A	30-07-1998	AU 5771898 A EP 0988378 A	18-08-1998 29-03-2000
WO 9522625 A	24-08-1995	US 5605793 A AU 703264 B AU 2971495 A CA 2182393 A CN 1145641 A EP 0752008 A EP 0934999 A JP 10500561 T US 6132970 A US 5830721 A US 5811238 A US 6117679 A US 5837458 A	25-02-1997 25-03-1999 04-09-1995 24-08-1995 19-03-1997 08-01-1997 11-08-1999 20-01-1998 17-10-2000 03-11-1998 22-09-1998 12-09-2000 17-11-1998

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- (21) International Application Number: PCT/US01/40091
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60/197,851 14 April 2000 (14.04.2000) US
- (71) Applicant (for all designated States except US): XENCOR, INC. [US/US]; 111 W. Lemon Avenue, Monrovia, CA 91016 (US).
- (72) Inventor; and
- (75) Inventor/Applicant (for US only): DAHIYAT, Bassil, I. [US/US]; 4413 San Andreas Avenue, Los Angeles, CA 90065 (US).
- (74) Agent: TRECARTIN, Richard, F.; Flehr Hohbach Test Albritton & Herbert LLP, Suite 3400, 4 Embarcadero Center, San Francisco, CA 94111-4187 (US).
- (81) Designated States (*national*): AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, BZ, CA, CH, CN, CR, CU, CZ, DE, DK, DM, DZ, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, TZ, UA, UG, US, UZ, VN, YU, ZA, ZW.
- (84) Designated States (*regional*): ARIPO patent (GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZW), Eurasian patent (AM, AZ, BY, KG, KZ, MD, RU, TJ, TM), European patent (AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, TR), OAPI patent (BF, BJ, CF, CG, CI, CM, GA, GN, GW, ML, MR, NE, SN, TD, TG).
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- For two-letter codes and other abbreviations, refer to the "Guidance Notes on Codes and Abbreviations" appearing at the beginning of each regular issue of the PCT Gazette.

(54) Title: PROTEIN DESIGN AUTOMATION FOR PROTEIN LIBRARIES

(57) Abstract: The invention relates to the use of protein design automation (PDA) to generate computationally prescreened secondary libraries of proteins, and to methods and compositions utilizing the libraries.

WO 01/59066 A3

INTERNATIONAL SEARCH REPORT

International Application No

PCT/US 01/40091

A. CLASSIFICATION OF SUBJECT MATTER

IPC 7 C12N15/10

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)

IPC 7 C12N

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)

WPI Data, CHEM ABS Data

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	WO 98 47089 A (CALIFORNIA INSTITUTE OF TECHNOLOGY) 22 October 1998 (1998-10-22) page 6, line 26 - line 30 ---	1
X	WO 98 32845 A (BIOINVENT INTERNATIONAL AB) 30 July 1998 (1998-07-30) the whole document ---	7,8
X	WO 95 22625 A (AFFYMAX) 24 August 1995 (1995-08-24) the whole document ---	7,8
	-/--	



Further documents are listed in the continuation of box C.



Patent family members are listed in annex.

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- * & * document member of the same patent family

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Name and mailing address of the ISA

European Patent Office, P.B. 5818 Patentlaan 2
NL - 2280 HV Rijswijk
Tel. (+31-70) 340-2040, Tx. 31 651 epo nl,
Fax: (+31-70) 340-3016

Authorized officer

Masturzo, P

INTERNATIONAL SEARCH REPORT

International Application No

PCT/US 01/40091

C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

Category	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
A	B I DAHIYAT & S L MAYO: "De novo protein design: fully automated sequence selection" SCIENCE., vol. 278, no. 5335, 3 October 1997 (1997-10-03), pages 82-87, XP002188179 AAAS. LANCASTER, PA., US ISSN: 0036-8075 cited in the application the whole document ---	1-9
A	B I DAHIYAT & S L MAYO: "Protein design automation" PROTEIN SCIENCE., vol. 5, no. 5, May 1996 (1996-05), pages 895-903, XP002073372 CAMBRIDGE UNIVERSITY PRESS, CAMBRIDGE., GB ISSN: 0961-8368 cited in the application the whole document ---	1-9
P,X	WO 00 23564 A (XENCOR INC.) 27 April 2000 (2000-04-27) the whole document -----	1-9

INTERNATIONAL SEARCH REPORT

Information on patent family members

International Application No

PCT/US 01/40091

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			WO 9847089 A1	22-10-1998
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			WO 9832845 A1	30-07-1998
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			EP 1157093 A1	28-11-2001
			WO 0023564 A2	27-04-2000

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- (26) Publication Language: English
- (30) Priority Data:
60/311,545 10 August 2001 (10.08.2001) US
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60/324,899 25 September 2001 (25.09.2001) US
60/351,937 25 January 2002 (25.01.2002) US
60/352,103 25 January 2002 (25.01.2002) US
- (71) Applicant (*for all designated States except US*): **XENCOR** [US/US]; 111 West Lemon Avenue, Monrovia, CA 91016 (US).
- (72) Inventors; and
- (75) Inventors/Applicants (*for US only*): **BENTZIEN, Joerg** [DE/US]; 66 Old Tarrytown Road, White Plains, NY 10603 (US). **DAHIYAT, Bassil, I.** [US/US]; 3829 Luna Court, Altadena, CA 91001 (US). **DESJARLAIS, John** [US/US]; 2096 Crary Street, Pasadena, CA 91104 (US). **HAYES, Robert, J.** [GB/US]; 64 North Mar Vista, #211, Pasadena, CA 91106 (US). **VIELMETTER, Jost** [DE/US]; 495 Alameda Street, Altadena, CA 91001 (US).
- (74) Agents: **TRECARTIN, Richard, F. et al.**; Dorsey & Whitney LLP, 4 Embarcadero Center, Suite 3400, San Francisco, CA 94111 (US).
- (81) Designated States (*national*): AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NO, NZ, OM, PH, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TN, TR, TT, TZ, UA, UG, US, UZ, VN, YU, ZA, ZM, ZW.
- (84) Designated States (*regional*): ARIPO patent (GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZM, ZW), Eurasian patent (AM, AZ, BY, KG, KZ, MD, RU, TJ, TM), European patent (AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, SK, TR), OAPI patent (BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG).
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(54) Title: PROTEIN DESIGN AUTOMATION FOR PROTEIN LIBRARIES

(57) Abstract: The invention relates to the use of protein design automation (PDATM) to generate computationally prescreened secondary libraries of proteins, and to methods and compositions utilizing the libraries.



WO 2003/014325 A3

INTERNATIONAL SEARCH REPORT

International application No.

PCT/US02/25588

A. CLASSIFICATION OF SUBJECT MATTER

IPC(7) : G01N 31/00, 33/48

US CL : 702/19,22

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)

U.S. : 702/19,22

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practicable, search terms used)
STN on line

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	US 6,269,312 B1 (MAYO et al.) July 31 2001, see claims 1-23.	1-6
X	WO 98/47089 A1 (CALIFORNIA INSTITUTE OF TECHNOLOGY), 22 October 1998, claims 1-16	1-6
X	DESJARLAIS et al. De novo design of the hydrophobic cores of proteins. Protein Science 1995, Vol. 4, pages 2006-2018, entire document.	1-7
X	FECHTELER, T. et al. Prediction of protein three-dimensional structures in insertion and deletion regions: A procedure for searching databases of representative protein fragments using geometric scoring criteria. Journal of Molecular Biology. 1995, Vol. 253, No. 1, pages 114-131, entire document.	83-96
X	WALLACE et al. Derivation of 3D coordinate templates for searching structural databases: Application to Ser-His-Asp catalytic triads in the serine proteinases and lipases. Protein Science. 1996, Vol. 5, pages 1001-1013, specifically, pages 1009-1011.	4
X	US 5,878,373 A (COHEN et al) 02 March 1999, claim 1.	16-29, 97-111
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Y		15



Further documents are listed in the continuation of Box C.



See patent family annex.

* Special categories of cited documents:		"T"	later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention
"A"	document defining the general state of the art which is not considered to be of particular relevance	"X"	document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone
"B"	earlier application or patent published on or after the international filing date	"Y"	document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art
"L"	document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)	"&"	document member of the same patent family
"O"	document referring to an oral disclosure, use, exhibition or other means		
"P"	document published prior to the international filing date but later than the priority date claimed		

Date of the actual completion of the international search

05 February 2003 (05.02.2003)

Date of mailing of the international search report

27 MAR 2003

Name and mailing address of the ISA/US

Commissioner of Patents and Trademarks

Box PCT

Washington, D.C. 20231

Facsimile No. (703)305-3230

Authorized officer

Michael Bohn

Telephone No. (703) 308-0196

INTERNATIONAL SEARCH REPORT

PCT/US02/25588

C. (Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	US 5,265,030 A (SKOLNICK et al) 23 November 1993, columns 2-8, claims 1-8	16-29, 30-47

INTERNATIONAL SEARCH REPORT

International application No.

PCT/US02/25588

Box I Observations where certain claims were found unsearchable (Continuation of Item 1 of first sheet)

This international report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:

1. ☐ Claim Nos.:
because they relate to subject matter not required to be searched by this Authority, namely:
2. ☒ Claim Nos.: 13 and 14 (in-part)
because they relate to parts of the international application that do not comply with the prescribed requirements to such an extent that no meaningful international search can be carried out, specifically:
The subject matter is not clearly defined
3. ☐ Claim Nos.:
because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).

Box II Observations where unity of invention is lacking (Continuation of Item 2 of first sheet)

This International Searching Authority found multiple inventions in this international application, as follows:
Please See Continuation Sheet

1. ☒ As all required additional search fees were timely paid by the applicant, this international search report covers all searchable claims.
2. ☐ As all searchable claims could be searched without effort justifying an additional fee, this Authority did not invite payment of any additional fee.
3. ☐ As only some of the required additional search fees were timely paid by the applicant, this international search report covers only those claims for which fees were paid, specifically claims Nos.:
4. ☐ No required additional search fees were timely paid by the applicant. Consequently, this international search report is restricted to the invention first mentioned in the claims; it is covered by claims Nos.:

Remark on Protest

☐
☐

The additional search fees were accompanied by the applicant's protest.

No protest accompanied the payment of additional search fees.

INTERNATIONAL SEARCH REPORT

BOX II. OBSERVATIONS WHERE UNITY OF INVENTION IS LACKING

This application contains the following inventions or groups of inventions which are not so linked as to form a single general inventive concept under PCT Rule 13.1. In order for all inventions to be examined, the appropriate additional examination fees must be paid.

Group I, claim(s) 1-3, 5-6, drawn to a method of determining an optimum product employing a computer program wherein a group of potential rotamers are determined or calculated.

Group II, claim(s) 4-6, drawn to a method for generating a set of optimized sequences executed by a computer program wherein a potential amino acids in the variable positions of the sequence is determined.

Group III, claim(s) 7,9, drawn to a method for generating a secondary library by generating a list of primary variant positions.

Group IV, claim(s) 8, 10-12, drawn to a method for generating a secondary library by generating a probability distribution of amino acids.

Group V, claim(s) 13, drawn to a composition comprising a plurality of secondary variant proteins.

Group VI, claim(s) 14, drawn to a composition comprising of a plurality of nucleic acid.

Group VII, claim(s) 15, drawn to a method for generating a secondary library of scaffold protein by using a first library rank-ordered list of scaffold protein primary variants.

Group VIII, claim(s) 16-29, 31-47, 50-51, drawn to a method of generating an optimized protein sequence executed by a computer program using sequence alignment of the proteins and a pseudo-energy function calculation or steps.

Group IX, claim(s) 30, 44, 46, 50-51, drawn to a method of generating an optimum protein by a computational method without using a computer program employing numerous process steps such as sequence alignment of related proteins, frequency of occurrence and other steps as recited.

Group X, claim(s) 48-51, drawn to a method of generating optimized protein sequences using (manual) computational method using substitution matrix.

Group XI, claim(s) 52-67, drawn to a method executed by a computer program including the step of using coordinates for the scaffold protein and scoring functions to generate a decoy sequence and comparative scoring.

Group XII, claim(s) 68, 70-82, drawn to a method of generating an alternate variable protein sequence using a computer program including the step of applying a defined energy state to a variable amino acid position of the protein scaffold.

Group XIII, claim(s) 69-71, 73, 81-82, drawn to a method of generating a variable protein sequence executed by computer program including the step of applying a probability parameter.

Group XIV, claim(s) 83-96, drawn to a method executed by a computer program wherein a set of coordinates are imported into a scaffold protein and employing a clustering algorithm.

Group XV, claim(s) 97-111, drawn to a method of identifying a protein with a similar conformation as the target protein.

Group XVI, claim(s) 113-116, drawn to a method of generating a variant protein sequence libraries by polymerize reaction.

The inventions listed as Groups I-II, VIII, XI, XII, XIII, XIV do not relate to a single general inventive concept under PCT Rule 13.1 because, under PCT Rule 13.2, they lack the same or corresponding special technical features for the following reasons: each of these methods would employ different programs since different parameters are required to achieve an optimum protein

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product. For example, the method of Group I would require a program to calculate the rotamers that would lead to an optimum product. The method of Group II requires a program for the presence or absence of an amino acid residue in a scaffold protein position. Thus, these methods would lack the same special technical features of a resultant product and/or method steps.

The inventions listed as Groups III, IV and VII do not relate to a single general inventive concept under PCT Rule 13.1 because, under PCT Rule 13.2, they lack the same or corresponding special technical features for the following reasons: the method of Group III generates a secondary library employing different method steps from those of Groups IV and VII. Thus, there are no corresponding special technical features for the different method steps resulting in different secondary library compositions.

The inventions listed as Groups V and VI do not relate to a single general inventive concept under PCT Rule 13.1 because, under PCT Rule 13.2, they lack the same or corresponding special technical features for the following reasons: Group V is drawn to a composition comprising of a plurality of variant proteins that lack the technical features of Group VI composition relating to a structurally different plural nucleic acid compounds. Because of the degeneracy of the nucleic acid triplet different protein products may be encoded by the nucleic acids..

The inventions listed as Groups IX and X do not relate to a single general inventive concept under PCT Rule 13.1 because, under PCT Rule 13.2, they lack the same or corresponding special technical features for the following reasons: Groups IX employs different process steps such as alignment and frequency of occurrence which does not correspond to the process step of Group X using substitution of residues in the scaffold protein region.

The inventions listed as Groups XV and XVI do not relate to a single general inventive concept under PCT Rule 13.1 because, under PCT Rule 13.2, they lack the same or corresponding special technical features for the following reasons: Groups XV and XVI are drawn to two different methods resulting in two different products. Group XVI uses polymerase reaction while Group XV employs the conformation of a target that would generate two different libraries.

The inventions listed as Groups (V, VI) and (I-IV and VII-XVI) do not relate to a single general inventive concept under PCT Rule 13.1 because, under PCT Rule 13.2, they lack the same or corresponding special technical features for the following reasons: Groups V and VI are drawn to compositions which lack the technical features of the processes of Groups I-IV and VII-XVI.

The inventions listed as Groups I-IV and VII-XVI do not relate to a single general inventive concept under PCT Rule 13.1 because, under PCT Rule 13.2, they lack the same or corresponding special technical features for the following reasons: these groups are drawn to different methods resulting in different optimized protein or libraries. For example, Group I employs computer to generate proteins. Group III, for example, relate to a non-computer method of generating secondary libraries. (See the above groupings of the different method Groups).

This application contains claims directed to more than one species of the generic invention. These species are deemed to lack unity of invention because they are not so linked as to form a single general inventive concept under PCT Rule 13.1.

In order for more than one species to be examined, the appropriate additional examination fees must be paid. The species are as follows:

Species:

- A). Frequency Calculation (claims 17-22).
- B). Scoring function (claim 45).
- C). Subset (claim 63).
- D). Identifying means (claims 109 or 110).

The species listed above do not relate to a single general inventive concept under PCT Rule 13.1 because, under PCT Rule 13.2, the species lack the same or corresponding special technical features for the following reasons: each of the species recited in each subgroups A-D do not have the same or corresponding technical features as each of the species in e.g., Group A involves different steps of calculating the frequency occurrence of an amino acid residue in the scaffold position. For example, the method by which a homologous amino acid residue in one or more position of the scaffold protein would not determine or relate to the method of

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determining the structure (i.e., conformational) or function of the variable protein. Likewise, the species recited in subgroup D wherein a protein is identified by searching the public databases would lack the special technical features of identifying said protein using dynamic computer programming algorithm.

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